

Development and Implementation of Vaccine Made in Third World

MK Bhan, New Delhi, India

Partners

Public Sector

USA Roger Glass, Harry Greenberg, Richard L Ward

India C Durga Rao, Nita Bhandari, Pratima Ray,
Ramesh Kumar, MK Bhan

Non Government Sector

Society for Applied Studies, New Delhi

PATH, USA

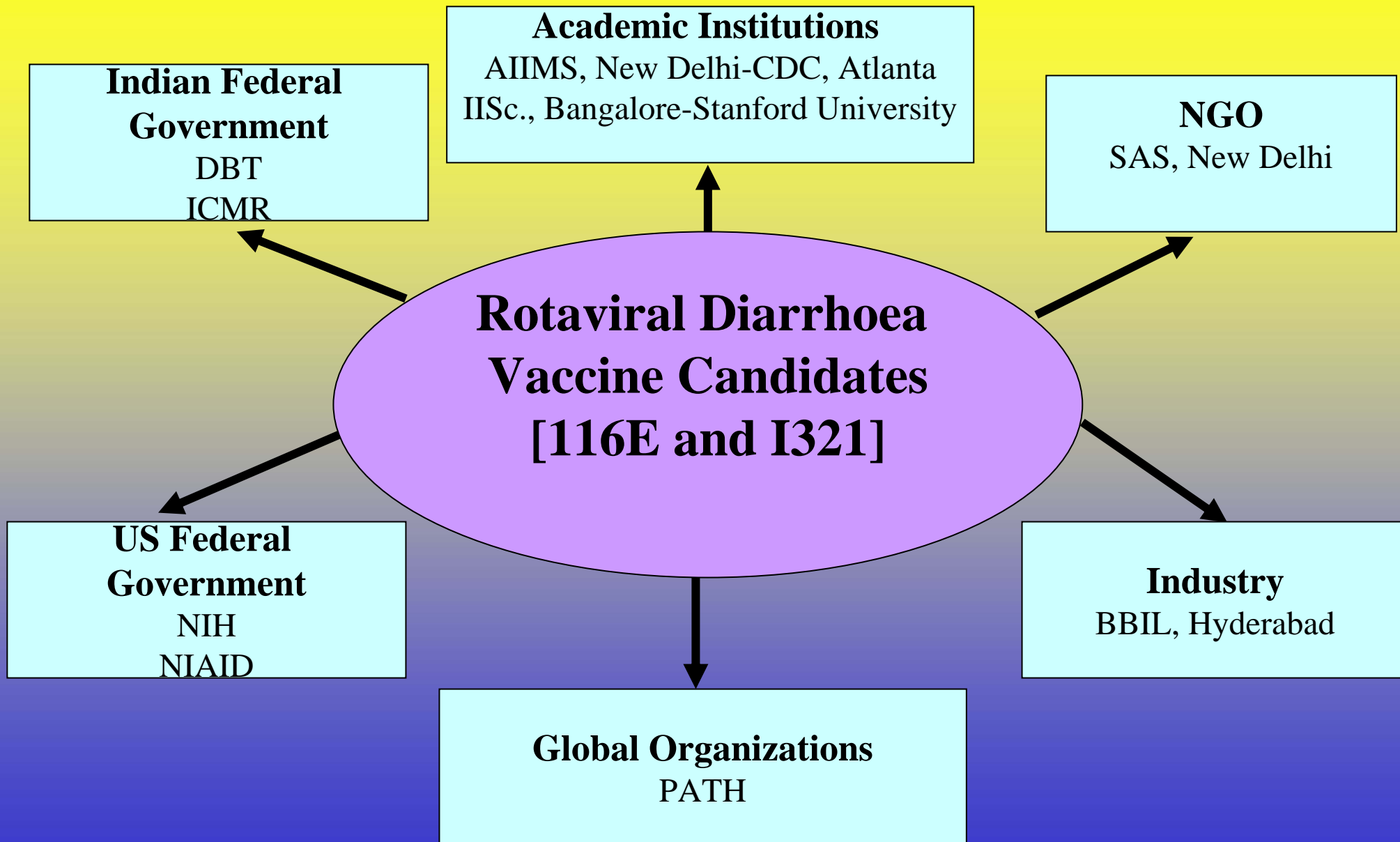
BBIL, Hyderabad

Clinical trials

Management and finance

Manufacturing

Rotaviral Diarrhoea Vaccine Development



Studies with Natural Rotavirus Infection in Delhi and Bangalore

- Neonatal infections with rotavirus common.
- Natural neonatal infection with RV associated with significant and prolonged viral shedding in Delhi and Bangalore.
- ≥ 4 fold rise in RV specific serum and salivary IgA in over half the neonatally infected infants.
- Neonatal infection protects (46%) against subsequent rotavirus diarrhea over 2 year period in Delhi.
- Evidence of protection also recently shown from Bangalore. following neonatal infection.

Nosocomial neonatal infection with 116E at AIIMS is immunogenic

- Specific IgA response
 - serum 56%
 - saliva 68%
- Neutralizing antibody response
 - serum 37%
 - saliva 56%

JID 1988, Clin Diag Lab Immunol 1998

Characteristics of the AIIMS neonatal strain 116E

- Bovine-human rotavirus reassortant:
P8 [11] G9
- VP6, NSP1, NSP4:
- Human rotavirus origin

J Clin Microbiol 1994, Virus Genes 1997

- Neonatal strain I321 from Bangalore is characterized as G10P11
- Strain contains 2 segments of human rotavirus origin and 9 segments of bovine origin including those encoding VP4 and VP7

Lack of maternal antibody may predispose to 116E neonatal infection

	Cord blood neutralizing antibody to 116E ≥ 200
Infected with 116E	7/18 (39%)
Infected with other rotaviruses	10/12 (83%)
Non-infected	15/20 (75%)

Clin Diag Lab Immunol 1998

Rotavirus Serotypes: India 1996-8

P types

53% common P

24% P6 : 11% with common G
 9% with G9
 4% with mixed or NT

G types

64% common G

17% G9 : 9% with P6
 5% with P8
 3% with mixed or NT

Multicenter study: AIIMS-CDC collaboration

Experimental live virus vaccine pool lot 116E-I and I321 prepared by
Dyna Corp PRI with NIH assistance

	116E	I321
PAGMK	2	2
Ma104	7	8
SPAGMK	10	8
Vaccine potency	2.0×10^6 FFu/ml	2.2×10^6 FFu/ml

Safety Studies in Adults and Children in Cincinnati

Adult, children and infant studies in India using Dyna Corp vaccine

Infant Safety Study of Candidate Vaccines 116E and I321 in Delhi

Key features

- Randomized controlled three cell trial
- Single dose 10^5 FFu
- Subjects: 90 healthy, non malnourished infants aged 8 weeks
- Period: January to May 2005
- Site: Low to middle income urban
- Placebo: Crystal of potassium permanganate added to sodium bicarbonate buffer

Trial Profile

Total households surveyed
50,000

Infants ≤ 14 days eligible for screening
645

Screened at 6 weeks of age
435

Based on screening, total eligible for enrollment
134

Enrolled and immunized at 8 weeks of age
90

Excluded
Refusals: 104
Gone to village: 89
Child ill: 12
Dead: 5

Excluded at
Interview: 59
Examination: 36
Lab investigations: 200
Refused participation: 6

Reason for exclusion
On medication: 25
Refusals: 17
Enrollment completed: 2

Placebo
30

I 321
30

116 E
30

Completed 28 days followup: 28

Completed 28 days followup: 27

Completed 28 days followup: 28

n=2
Moved away at day 26: 1
Moved away at day 27: 1

n=3
Refused further participation at day 2: 1
Moved away at day 19: 1
Moved away at day 27: 1

n=2
Moved away at day 27: 2

Participants Experiencing Mild (Grade 1) or Moderate (Grade 2) or Severe (Grade 3) Adverse Events in First 14 Days Possibly or Remotely Related to Administration of the Vaccines or Placebo

Illness episodes	Placebo (n=30)	I321 (n=29)*	116E (n=30)
History of fever	5	1	6
Measured temperature >99.5°F (>37.5° C)	1	-	2
Irritable infant	3	-	1
Diarrhea without vomiting	3	8	5
Diarrhea with vomiting	2	-	-
Diarrhea and stool positive for vaccine virus	-	-	2 [†]
Abdominal distension	1	-	-
Inconsolable crying	2	1	-
Vomiting only	-	-	2
Skin rash	-	1	1

*One infant refused participation on day 2 post vaccination; [†]G9[P11]

Note: 1 infant each in the placebo and I321 groups had 2 episodes of fever, another infant in the I321 group had 2 episodes of diarrhea. Two infants in the 116E group had two episodes of diarrhea each

Stool Positivity for Rotavirus Antigen by ELISA Pre-immunization and Days 3, 7 and 28 Post Administration of Vaccines or Placebo

	Placebo	I321	116E
	(n=30)	(n=30)	(n=30)
Day 0	-	-	1
	(n=30)	(n=30)	(n=30)
Day 3	1	1	10
	(n=30)	(n=29)	(n=30)
Day 7	1	1	7
	(n=30)	(n=29)	(n=30)
Day 3 or 7	2	1	12
	(n=30)	(n=28)	(n=30)
Day 3 or 7 or 28	2 (G12[P6]: 1, NS:1)	2 (G9[P8]:1, NS:1)	12 (G9[P11]:11, G9[P6]:1)

Figures in parenthesis indicate shedding of vaccine virus as per G and P types. NS: sample not sufficient

Enrolled Infants with ≥ 4 Fold Rise in Rota Specific Serum IgA Between Baseline and Day 28 Post Administration of Vaccines or Placebo

	Placebo (n=30)	I321 (n=28) ^a	116E (n=30)
Number (%)	6 (20.0)	11 (39.3)	22 (73.3) ^b
95% CI	7.7% to 38.5%	21.5% to 59.4%	54.1% to 87.7%

^aTwo day 28 samples were not available

^bChi-square for trend, $p < 0.0001$

In the 116E group, 11/30 infants shed the vaccine virus in stools and seroconverted, 1/30 shed a wild rotavirus strain and seroconverted and 10/30 only seroconverted

Immunogenicity of live oral human rota virus vaccine in previously uninfected infants from US and India (randomized double-blind placebo-controlled trials)

Country	Age of infants vaccinated (weeks)	RN vaccine candidate	Dose of vaccine (P.f.u.)	Antirotavirus IgA Antibody (units / ml) response (n%)		Neutralizing Antibodies
				after dose1	after dose2	
USA (Bernstein et al, 1999)	10-16	attenuated 89-12	10 ⁵	98/107 (91.6)		74/107 (69.2)
USA (Bernstein et al, 1998)	6-26	attenuated 89-12	10 ⁵	16/20 (80)	19/20 (95)	7/20 (35)
India	6-26	116E	10 ⁵			

116E VERO CELL CANDIDATE VACCINE

- Experimental live virus vero cell vaccine pool lot 116E prepared by M/s Bharat Biotech Intrl.Ltd. (BBIL) under supervision of the international rotavirus vaccine development group.
- Liquid, active biological ingredient of RV 116E strains bulk, stabilizer, antibiotics, and buffer solution.
- Vaccine stored at $-70^{\circ}\text{C} \pm 5^{\circ}\text{C}$ at BBIL

“A Double-Blind Randomized Placebo Controlled Dose Escalating Phase Ib/Ila Study to Evaluate the Safety and Immunogenicity of Live Attenuated Rotavirus Vaccine 116E in Healthy Non Malnourished Infants 8-20 Weeks of Age”

Objectives :

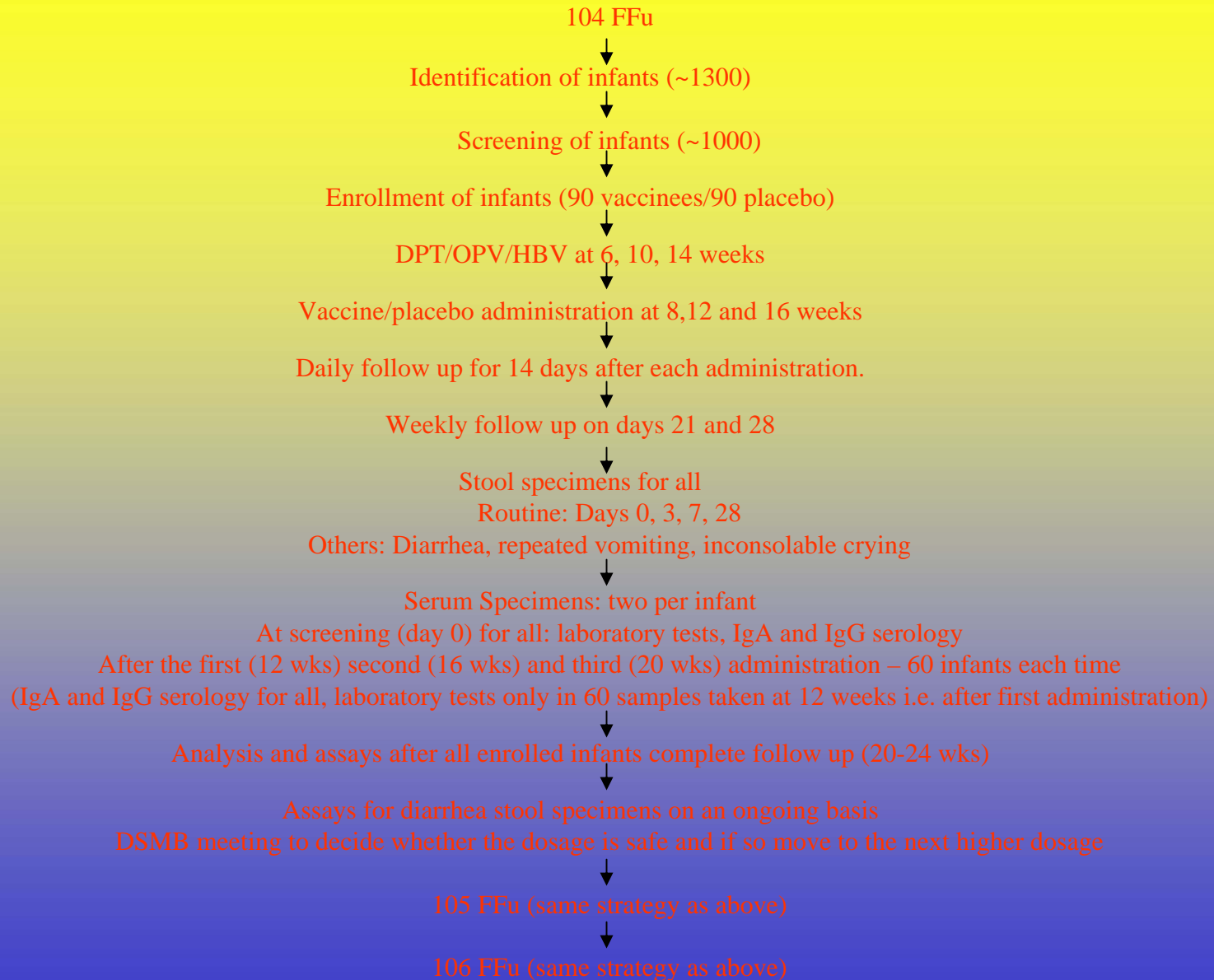
Primary

- To evaluate the safety of Vero cell based 116E rotavirus vaccine candidate strains administered three times orally at 4-week intervals at three dosage levels [10⁴, 10⁵ and 10⁶ fluorescence focus units (FFu)] in healthy non-malnourished infants 8 to 20 weeks of age.

Secondary

- To evaluate the immunogenicity of Vero cell based 116E rotavirus vaccine candidate strains administered three times orally at 4-week intervals at three dosage levels (10⁴, 10⁵ and 10⁶ FFu) in healthy non-malnourished infants 8 to 20 weeks of age.

FLOW CHART OF THE STUDY STRATEGY FOR EACH OF THE THREE DOSAGES 104, 105 AND 106

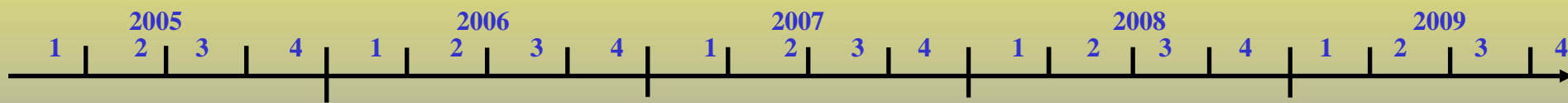


Clinical development, Overview

AGMK, NIH

Ph I Infants

Ph II b



Ph I Adults + Children

Ph 1 / 2 Infants (dose ranges)

Ph 2b or 3

Vero, BBIL

- **Potential gains of the global partnership**
 - **Capacity building and training**
 - **Pooling of expertise**

- **Monitoring and problem solving**
 - **Availability of critical biological reagents/material**
 - **Clinical development planning**
 - **Financial resources**
 - **High quality programme management.**

- **Challenges**

- Shifting from a science investigation model to product development programme required changing roles of partners
- Vaccine for Global use versus for National use.

CHALLENGES

BBIL

- **Quality human resource**
- **Leadership**
- **Clinical development expertise**
- **QA/QC**
- **Formulation and stability**
- **Mindset – Global versus National**
- **Pre-clinical testing**
- **Financial resources**
- **Emerging Competition**

CHALLENGES FOR CLINICAL TRIALS

- SAS is a not for profit structure;
Stability, retaining human resource, building capacity, Financial support in between trials.
Role of private CRO's
- Availability of laboratory over the years that can perform validated assays in large numbers in time.

ROLE OF REGULATORY AUTHORITIES

- DBT and ICMR arranged discussion on aprior approval of clinical development plan.
- DBT and ICMR generated decision making rules for Drug Controller General of India.
- DBT and ICMR created a policy for introduction of new vaccine in India.

FEW UNANSWERED QUESTIONS : CHALLENGES REGARDING THE NEXT GENERATION OF ROTAVIRUS VACCINES

- Will live oral rotavirus vaccines work well for children in the developing world?
- How safe will they be; intussusception issues.
- Will parents accept a vaccine for only 1 cause of childhood diarrhea?

***Thank
You***